
بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ
In the name of Allah
the Most Gracious
the Most Merciful
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seminar1

Apoptosis and cancer therapy

Presented by:Rostamy.A

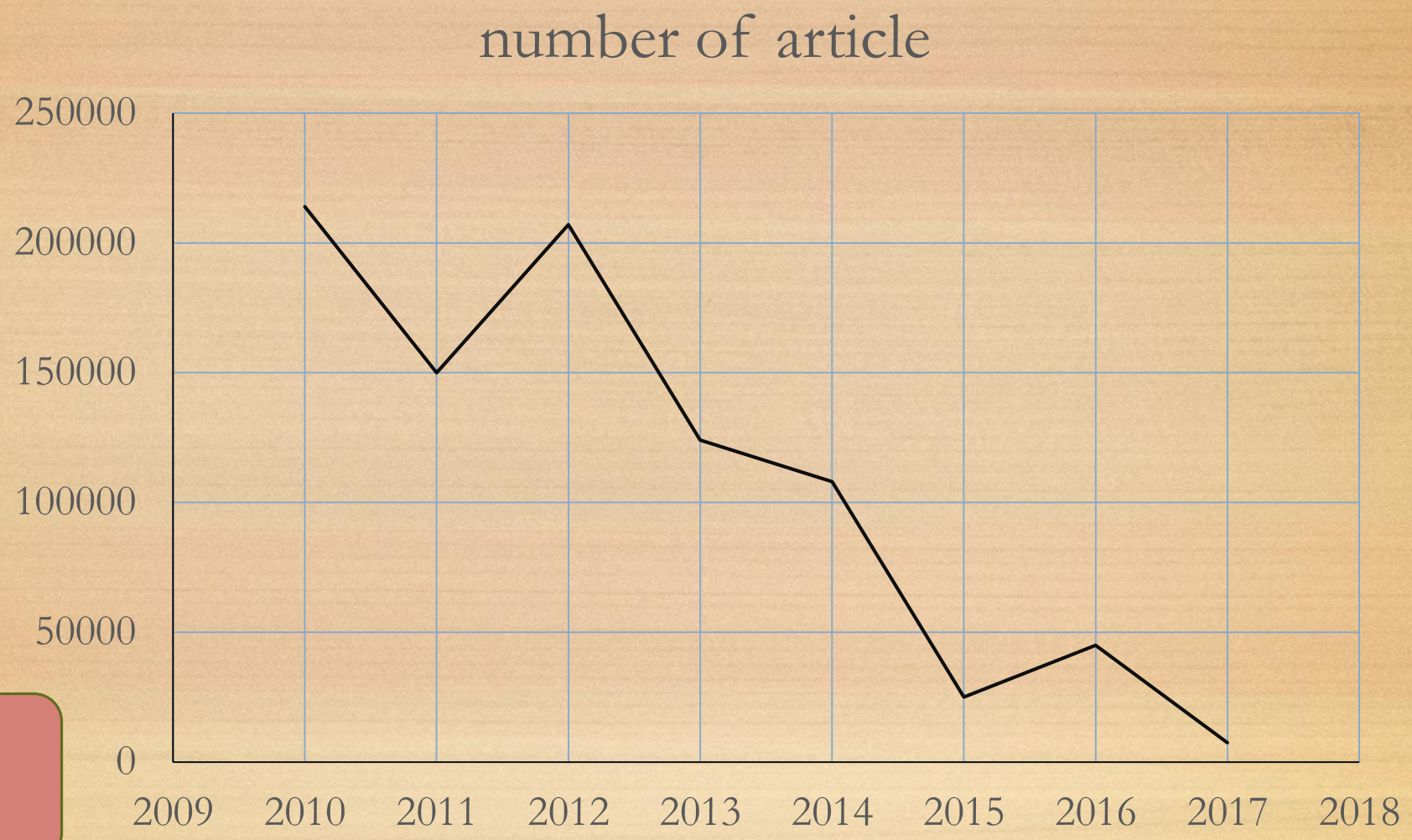
Under suppervision :Dr. Ahmadpour.

Paramedicine faculty

Qazvin university of medical science

contents

Apoptosis and cancer therapy



Source:google schoolar
Last updated:2017/4/14

Introduction

Apoptosis

The term "apoptosis" is derived from the Greek words "*απο*" and "*πτωσις*"

meaning "dropping off" and refers to the falling of leaves from trees in autumn.

Introduction

Morphological changes in apoptosis

Morphological alterations of apoptotic cell death that concern both the nucleus and the cytoplasm are

remarkably similar across cell types and species

Introduction

Morphological hallmarks of apoptosis in the nucleus are

chromatin condensation and nuclear fragmentation,

which are accompanied by

1)rounding up of the cell,

2)reduction in cellular volume (pyknosis)

3)retraction of pseudopodes

Introduction

Chromatin condensation starts at the periphery of the

1) nuclear membrane,

2) forming a crescent or

3) ring-like structure

Introduction

The chromatin further condenses

until it breaks up inside a cell with an intact membrane, a feature described as karyorrhexis

he plasma membrane is

intact throughout the total process

Introduction

At the later stage of apoptosis some of the morphological features include

1)membrane blebbing

2) ultrastrutural modification of cytoplasmic organelle

3)and a loss of membrane integrity(1)

Biochemical changes in apoptosis

1) activation of caspases,

2) DNA and protein breakdown and

3) membrane changes and recognition by phagocytic cells

Introduction

Early in apoptosis

here is expression of phosphatidylserine (PS) in the outer layers of the cell membrane

which has been "flipped out" from the inner layers. This allows early recognition of dead cells by macrophages,

resulting in phagocytosis without the release of pro-inflammatory cellular components

Introduction

Early in apoptosis

This is followed by a characteristic

breakdown of DNA into

large 50 to 300 kilobase pieces

Introduction

Later

there is

internucleosomal cleavage of DNA

into oligonucleosomes in multiples of

180 to 200 base pairs by

Endonucleases(2)

Introduction

Another specific feature of

apoptosis is the activation of a group of enzymes belonging to

to the cysteine protease family named caspases.

The "c" of "caspase" refers to a cysteine protease, while the "aspase" refers to the enzyme's unique property to cleave after aspartic acid residues

Introduction

Activated caspases

1)cleave many vital cellular proteins

2)and break up the nuclear scaffold and cytoskeleton.

3)They also activate DNAase, which further degrade nuclear DNA(3)

Introduction

Mechanisms of apoptosis

Caspases are central to the mechanism of apoptosis as they are both the

initiators and executioners

There are three pathways by which

caspases can be activated

Introduction

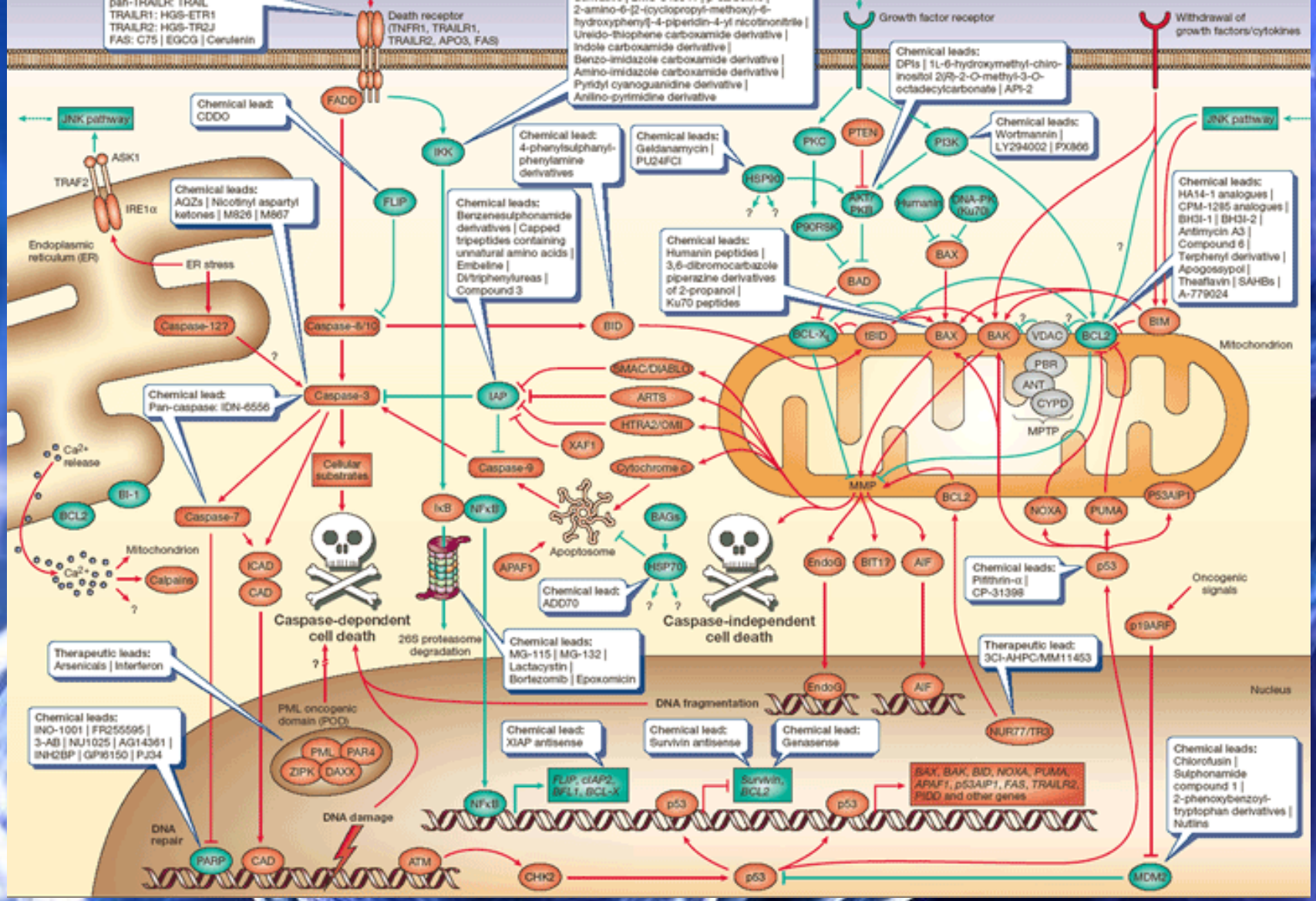
The two commonly described

initiation pathways are the

1)intrinsic (or mitochondrial)

2) and extrinsic (or death receptor)

3)A third less well-known initiation pathway is the intrinsic endoplasmic reticulum pathway(4)



Source:http://www.ufrgs.br

Last Updated:1395/12/12

The extrinsic death receptor pathway

Introduction

The extrinsic death receptor pathway

the best known death receptors is the type

1 TNF receptor (TNFR1)

and a related protein called Fas (CD95)

and their ligands are called TNF and Fas ligand (FasL) respectively

Introduction

The extrinsic death receptor pathway

These death receptors have an

1)intracellular death domain that recruits adapter proteins such as TNF receptor-

2)associated death domain (TRADD) and

3)Fas-associated death domain (FADD), as well as cysteine proteases like caspase 8

Introduction

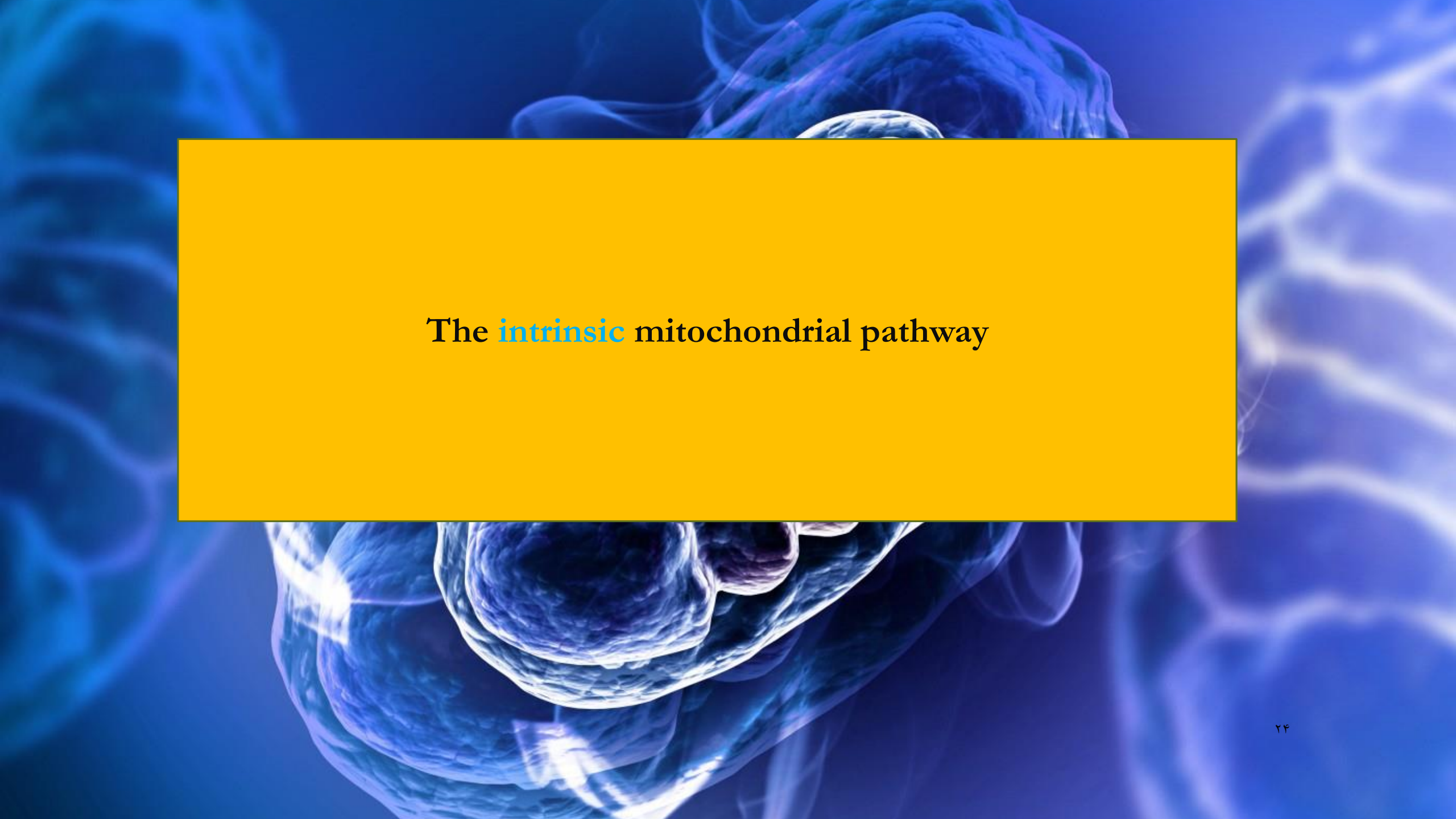
The extrinsic death receptor pathway

the whole ligand-receptor-adaptor protein complex is known as

the death-inducing signalling complex (DISC)

DISC then initiates the assembly

and activation of pro-caspase 8


The intrinsic mitochondrial pathway

The intrinsic mitochondrial pathway

Internal stimuli such as

1)irreparable genetic damage

2)hypoxia,

3)extremely high concentrations of cytosolic Ca^{2+}

4)and severe oxidative stress are some triggers of the initiation of the intrinsic mitochondrial pathwa

The intrinsic mitochondrial pathway

Regardless of the stimuli

this pathway is the result of

increased mitochondrial permeability and the release

of pro-apoptotic molecules such as cytochrome-c into the cytoplasm

Introduction

The intrinsic mitochondrial pathway

This pathway is closely regulated by a group of proteins belonging to the Bcl-2 family, named after the BCL2 gene originally observed at the

chromosomal breakpoint of the

translocation of chromosome 18 to 14

in follicular non-Hodgkin lymphoma

Introduction

The intrinsic mitochondrial pathway

There are two main groups of the Bcl-2 proteins

1)namely the pro-apoptotic proteins (e.g. Bax, Bak, Bad, Bcl-XBs, id, Bik, Bim and Hrk)

2)and the anti-apoptotic proteins (e.g. Bcl-2, Bcl-X_L, Bcl-W, Bfl-1 and Mcl-1)

Introduction

The intrinsic mitochondrial pathway

Other apoptotic factors that

are released from the mitochondrial intermembrane space into the cytoplasm include

1)apoptosis inducing factor (AIF)

2) second mitochondria-derived activator of caspase (Smac)

3) direct IAP Binding protein with Low pI (DIABLO)

4)and Omi/high temperature requirement protein A (HtrA2)

Introduction

The intrinsic mitochondrial pathway

Cytoplasmic release of

cytochrome c activates caspase 3 via the formation of

a complex known as apoptosome which is made up

1) cytochrome c

2) Apaf-1

3) and caspase 9

Introduction

The intrinsic mitochondrial pathway

Smac/DIABLO or Omi/HtrA2

promotes caspase activation by

binding to inhibitor of apoptosis proteins (IAPs)

which subsequently leads to disruption in the interaction of IAPs with caspase-3 or -9

Introduction

The intrinsic endoplasmic reticulum pathway

It is believed to be

caspase 12-dependent

and mitochondria-independent

When the ER is injured by

cellular stresses like

1)hypoxia

2)free radicals or

3)glucose starvation(5)

Introduction

Apoptosis and carcinogenesis

Disrupted balance of pro-apoptotic and anti-apoptotic proteins

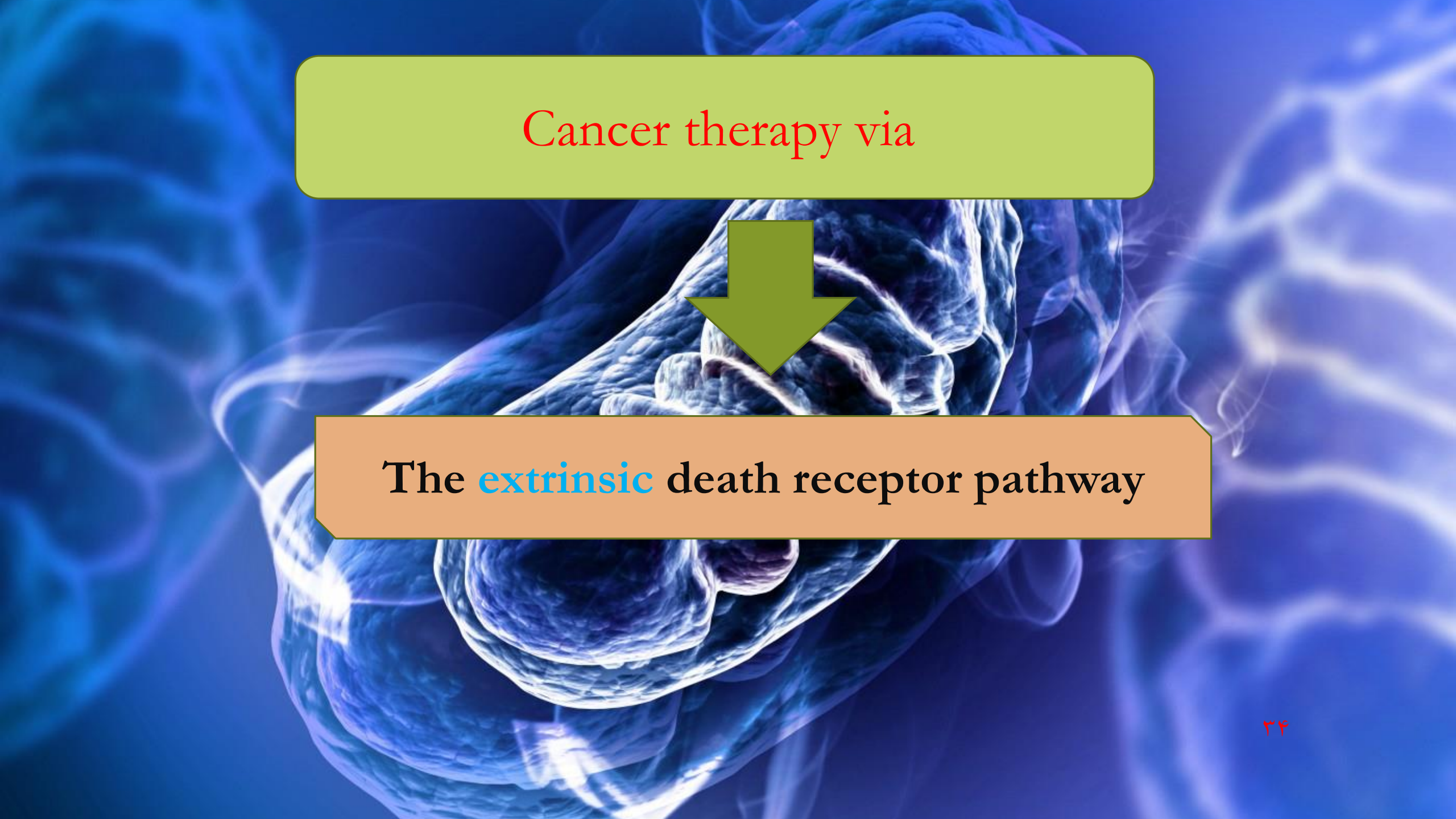
The Bcl-2 family of proteins

p53

(IAPs)

Reduced capsase activity

Impaired death receptor signaling(6)


Cancer therapy via
The extrinsic death receptor pathway

Discussion

RhApo2L/TRAIL effectively

induces apoptosis in vitro in a broad

spectrum of cancer cell lines, including

1)lung

2)colon

3)pancreas and

4)lymphoma

Discussion

RhApo2L/TRAIL also has demonstrated single-agent activity in vivo in preclinical tumor models based on

1)SCID

2)athymic nude mice bearing CRC

3)NSCLC

4)non-Hodgkin's lymphoma (NHL) xenografts.

Discussion

Preclinical Safety of rhApo2L/TRAIL

In the first of two studies, cynomolgus monkeys were administered rhApo2L/TRAIL at doses of.

0,
0.1,
1.0,
or 10 mg/kg/d

For

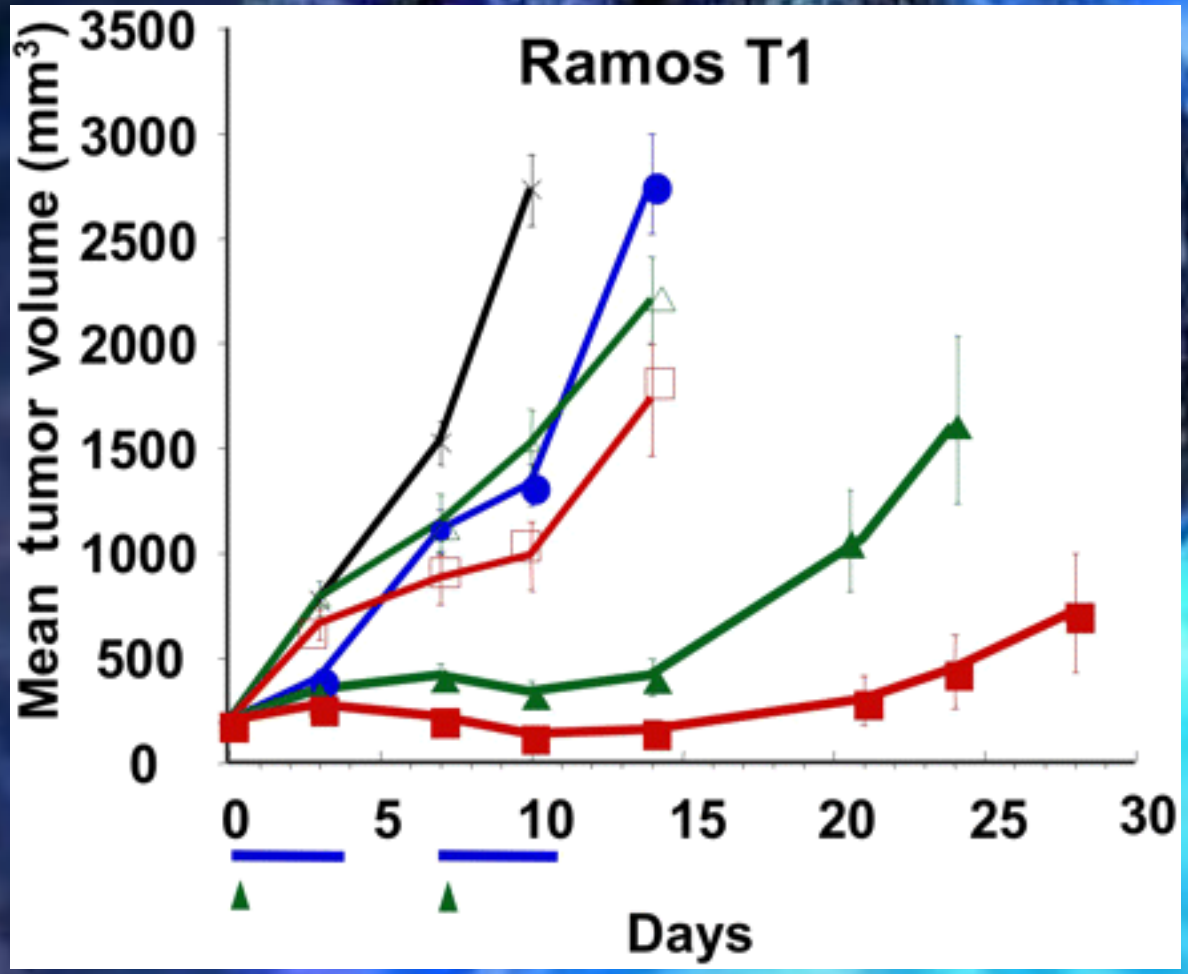
7 days

Discussion

Preclinical Safety of rhApo2L/TRAIL

Neither detectable signs of liver toxicity nor changes in liver enzyme activity were observed

no evidence of toxicity to any other major organ system or tissue was detected.(6)



http://www.bloodjournal.org/content/110/12/4037?sso-checked=true

LAST UPDETE:12/04/2017

Activity of rhApo2L/TRAIL and rituximab

1)Mice (n = 12 mice/group) were then treated with vehicle (black x),

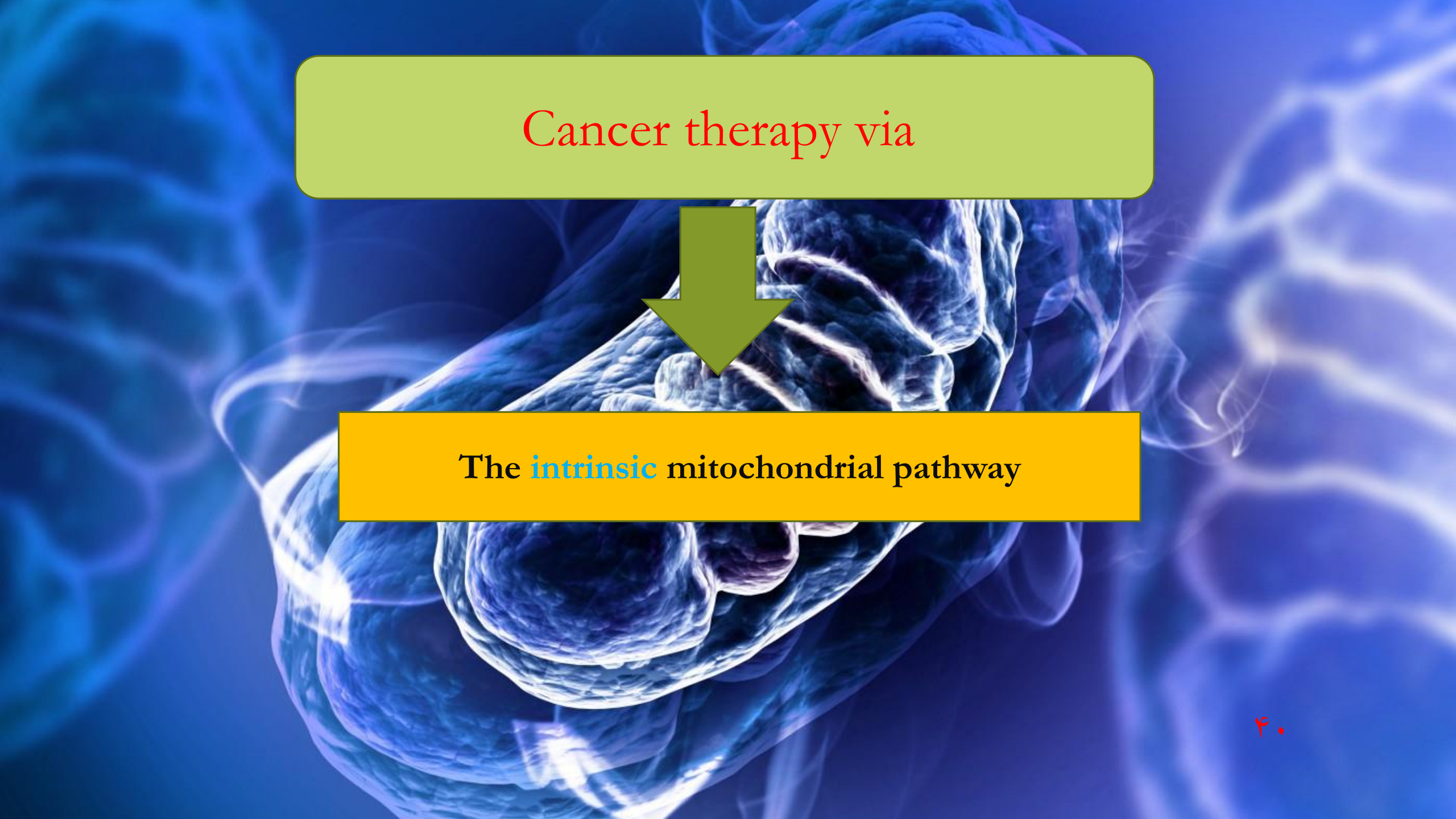
2)60 mg/kg rhApo2L/TRAIL (closed blue circle),

3)4 mg/kg rituximab (open green triangle),

4)10 mg/kg rituximab (open red square),

5)rhApo2L/TRAIL and 4 mg/kg rituximab (closed green triangle),

6)or rhApo2L/TRAIL and 10 mg/kg rituximab (closed red square).


Cancer therapy via
The intrinsic mitochondrial pathway

Discussion

Oxidative Stress

Oxidative stress is a biochemical condition that is characterized by the imbalance between

the presence of

relatively high levels of toxic reactive species

Discussion

Oxidative Stress

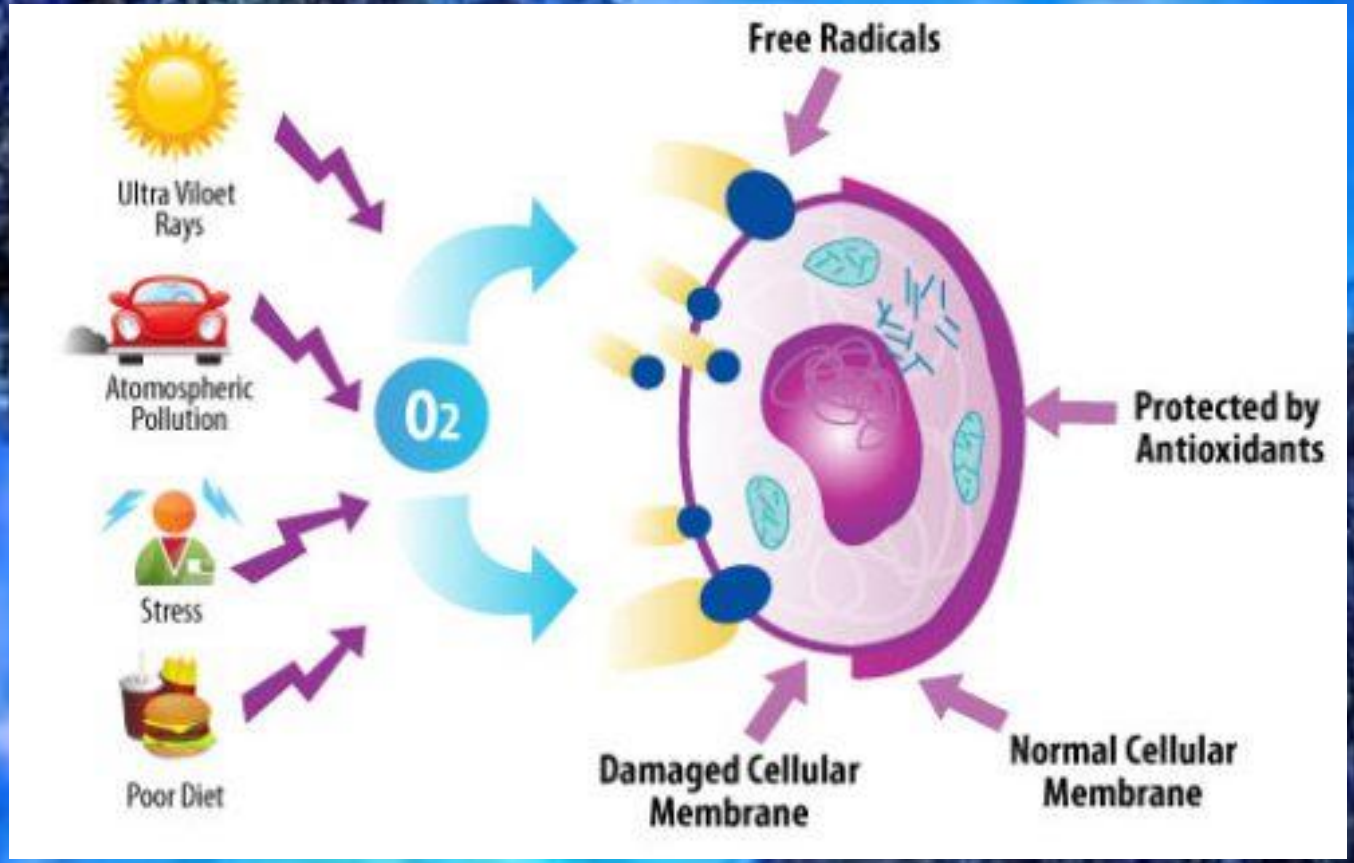
1)reactive oxygen species (ROS),

2)reactive nitrogen species (RNS),

3)and the antioxidative defense mechanisms.1–3
ROS and RNS

are organic or inorganic molecules that have an odd number of electrons

Oxidative Stress



http://www.in-corpore.ch/news/oxidative-stress-nutrition/

Last update:2017/04/14

Discussion

Oxidative Stress

The biological functions of oxidative stress

and its
potential role in cancer
development and progression

have been investigated for several decades.
Cancer itself induces oxidative stress

Discussion

Oxidative Stress

actually
ROS levels have been found to be significantly higher and

GPX and SOD activities significantly lower in cancer patients than controls(7)

Cell Proliferation

Cell Prolif., 2012, **45**, 487–498 doi: 10.1111/j.1365-2184.2012.00845.x

Programmed cell death pathways in cancer: a review of apoptosis, autophagy and programmed necrosis

L. Ouyang*,[2], Z. Shi†,‡,[2], S. Zhao†,[2], F.-T. Wang*,†, T.-T. Zhou§, B. Liu* and J.-K. Bao†

**State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China, †Key Laboratory of Bio-resources and Eco-environment, Ministry of Education, School of Life Sciences, Sichuan University, Chengdu, China, ‡School of Life Sciences, Guizhou Normal University, Guiyang, China, and §Shanghai Key Laboratory for Pharmaceutical Metabolite Research, School of Pharmacy, Second Military Medical University, Shanghai, China*

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Abstract

Programmed cell death (PCD), referring to apoptosis, autophagy and programmed necrosis, is proposed to be death of a cell in any pathological format, when mediated by an intracellular program. These three forms of PCD may jointly decide the fate of cells of malignant neoplasms; apoptosis and

Introduction: a brief overview of programmed cell death

Programmed cell death (PCD) may balance cell death with survival of normal cells; the equilibrium becomes disturbed and PCD plays key roles in ultimate decisions of cancer cell fate (1,2). Of note, apoptosis, autophagy and programmed necrosis are the three main forms of

Discussion

Oxidative Stress

It is well established that some chemotherapeutic agents and radiation therapy

generate ROS in patients during cancer therapy

Discussion

Oxidative Stress

Chemotherapy agents can be divided into several categories

1)alkylating agents (e.g., cyclophosphamide, ifosfamide)

2)anthracycline antibiotics which affect nucleic acids (e.g., doxorubicin, bleomycin)

3)platinum compounds (e.g., cisplatin)

Discussion

bcl2

BCL2 is known to

1)prevent programmed cell death

2)increase
metastatic potential

3)and promote resistance to
anticancer
therapy.

Discussion

bcl2

High expression of the BCL2 proto-oncogene is found in various solid tumours

G3139 is an antisense phosphorothioate oligodeoxynucleotide

that suppresses BCL2 expression

bcl2

Published in final edited form as:
Clin Cancer Res. 2009 February 15; 15(4): 1126–1132. doi:10.1158/1078-0432.CCR-08-0144.

Bcl-2 Inhibitors: Targeting Mitochondrial Apoptotic Pathways in Cancer Therapy

Min H. Kang[1,2] and **C. Patrick Reynolds**[1,3,4]

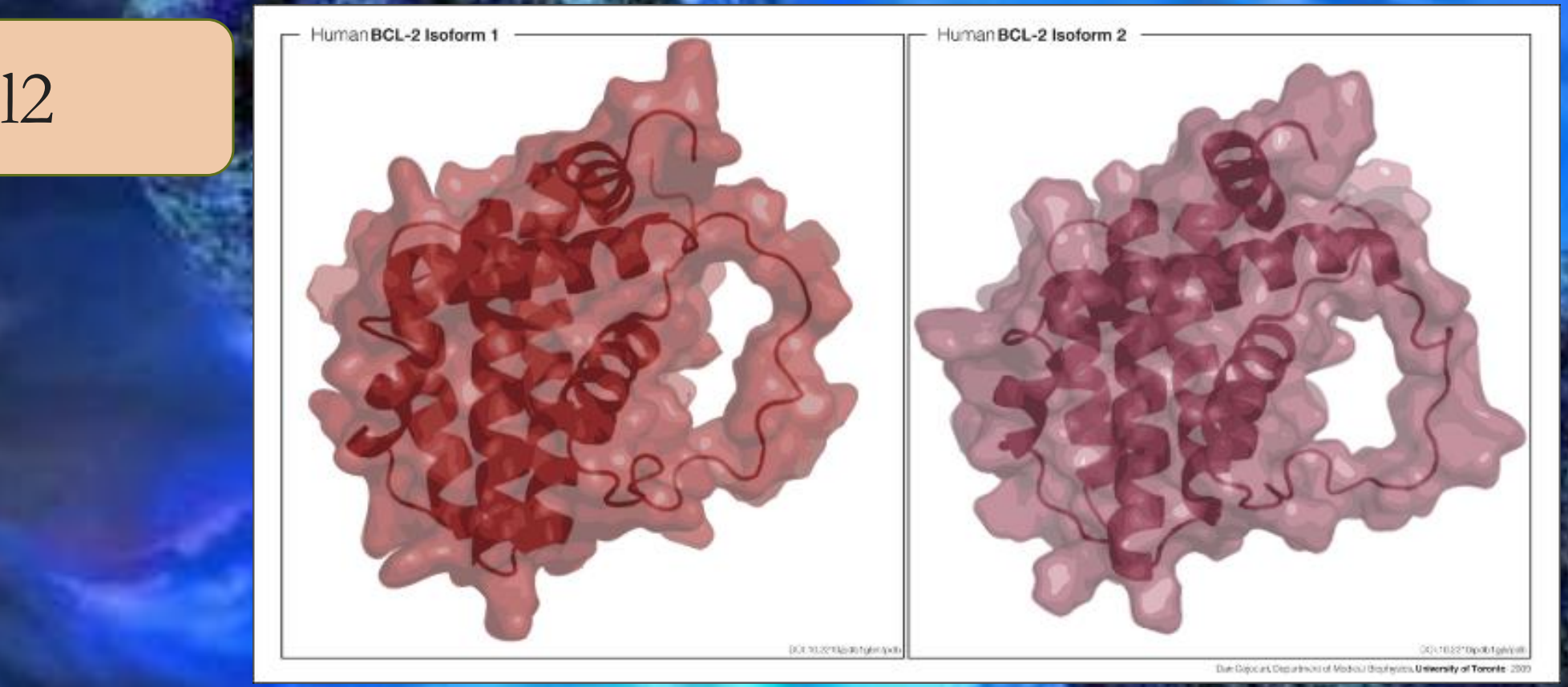
[1] Cancer Center and the Department of Cell Biology and Biochemistry, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas

[2] Department of Pharmacology, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas

[3] Department of Internal Medicine, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas

[4] Department of Pediatrics, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas

bcl2



Source: en.wikipedia.org/wiki/Bcl-2#/media/File:BCL-2_human.png

Last updated:12/04/2017

Discussion

bcl2

BCL2 antisense therapy is well tolerated

The first results of a phase I dose-escalation clinical trial evaluating subcutaneous administration of G3139(8)

Discussion

p53

One of the most advanced gene therapy agents used in the treatment of human cancer is

the replication-incompetent adenovirus that delivers a *p53* expression cassette, RPR/INGN201

Discussion

p53

Preclinical studies in human cell lines and
animals with head and neck cancers have shown

that the
p53 gene contained in RPR/INGN201 is efficiently
transcribed and translated into p53 protein

Discussion

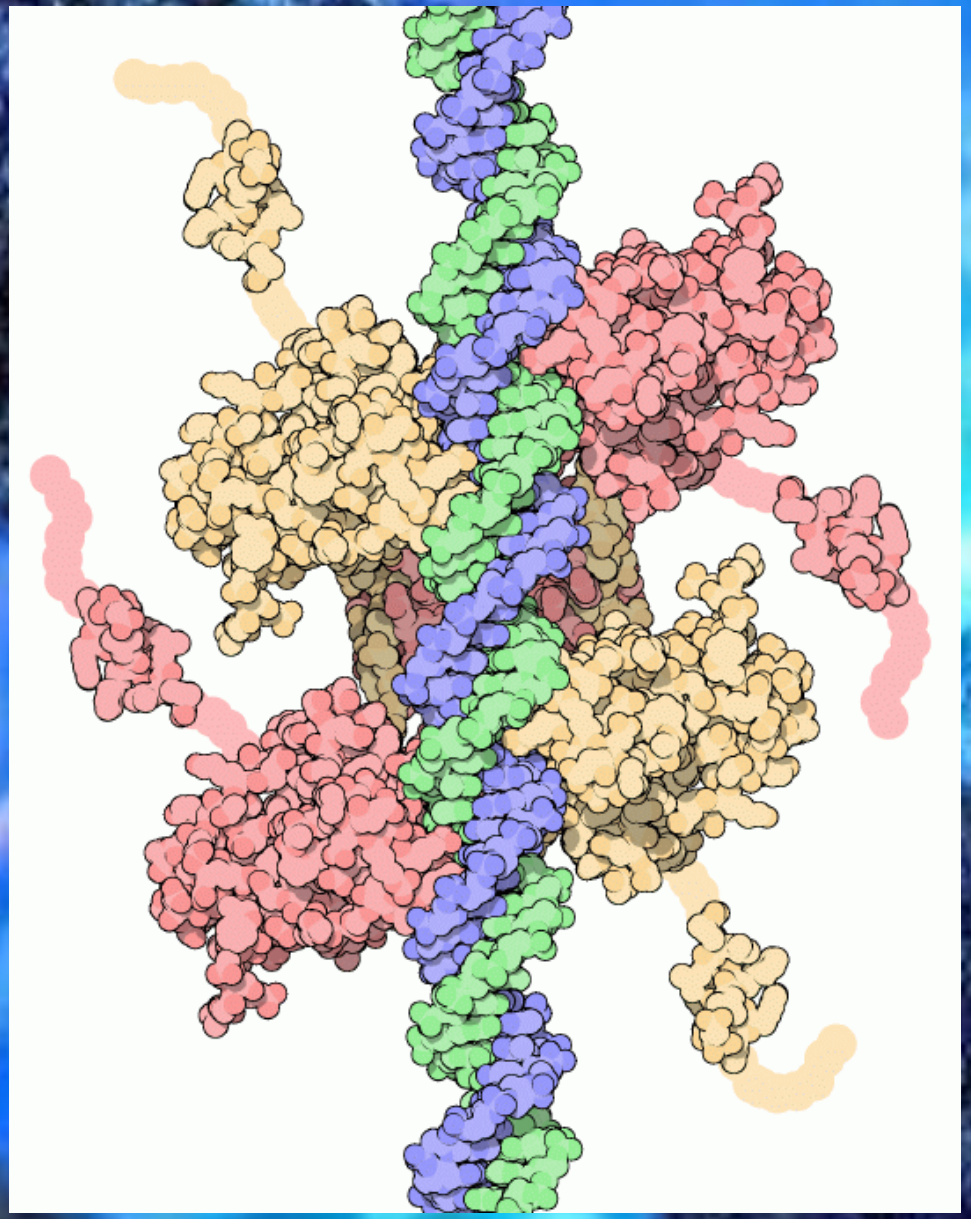
p53

Treatment with
RPR/INGN201

inhibited cell growth in human SCCHN
cell lines of diverse p53 status

and suppressed tumour growth in animal xenografts of human SCCHN through the apoptotic pathway and other effects, such as inhibition of angiogenesis.(9)

p53



https://pdb101.rcsb.org/motm/31

LAST UPDETED:12/04/2017

p53

http://www.dailymail.co.uk/health/article-3173307
LAST UPDETED:12/04/2017

Oncogene (2003) 22, 9030–9040

www.nature.com/onc

Control of apoptosis by p53

Jordan S Fridman[1,3] and Scott W Lowe*,[2]

[1]*Incyte Corporation, Wilmington, DE 19880*
[2]*Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA*

The p53 tumor suppressor acts to integrate multiple stress signals into a series of diverse antiproliferative responses. One of the most important p53 functions is its ability to activate apoptosis, and disruption of this process can promote tumor progression and chemoresistance. p53 apparently promotes apoptosis through transcription-dependent and -independent mechanisms that act in concert to ensure that the cell death program proceeds

most commonly inactivated tumor suppressor gene in human cancer (Hussain and Harris, 1998; Beroud and Soussi, 2003).

Although most of the attention on p53 has focused on its role in cancer, chronic activation of this key biological pathway may be equally as deleterious as its inactivation. In fact, hyperactivation of p53 has been associated with a variety of degenerative diseases such as

Discussion

CASPASE FAMILY

caspase-8 is mutated in different types of cancers

Soung and colleagues94 screened gastric carcinomas (162 cases),

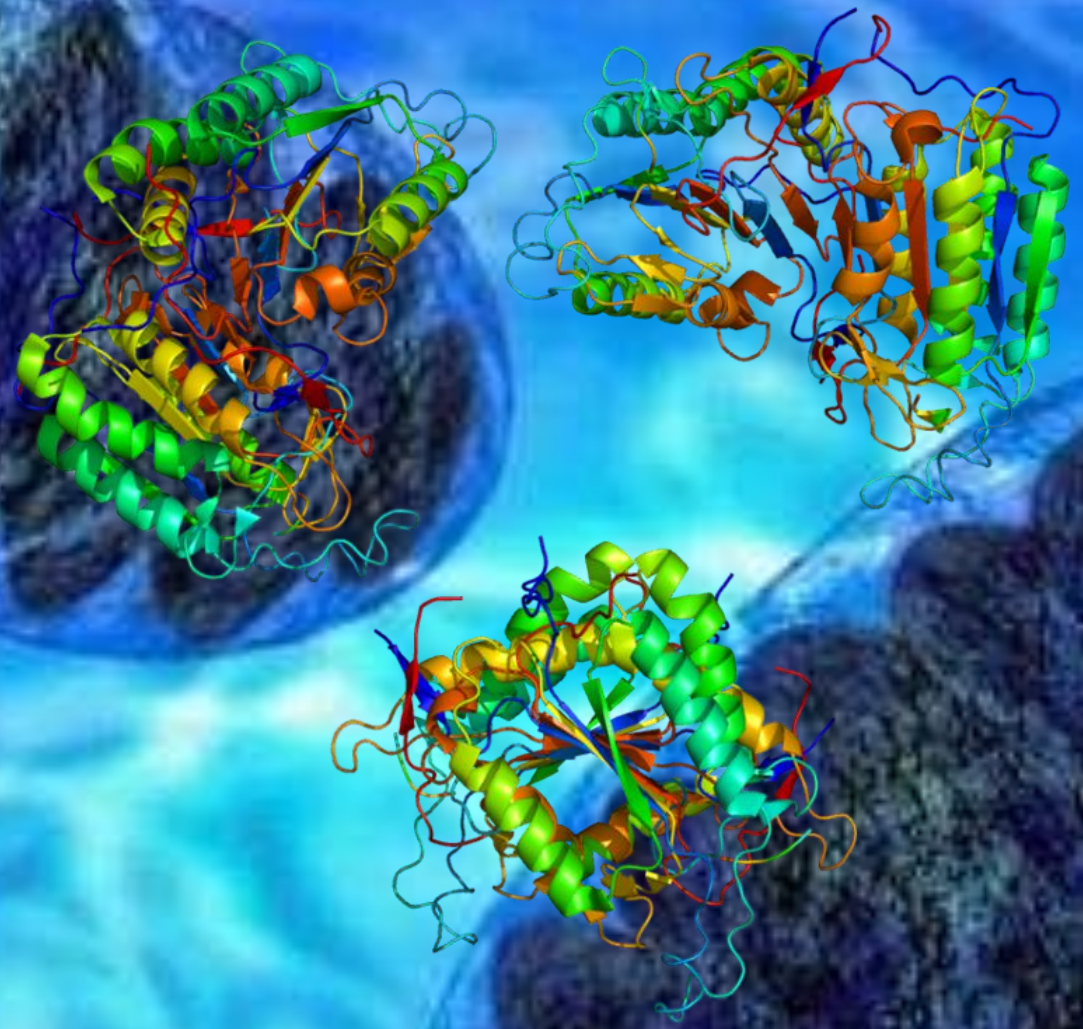
breast carcinomas (93 caspase),

non–small cell lung cancers (NSCLC) (185 cases),

and 88 acute leukaemias (88 cases)

for mutations within the caspase-8 gene using single strand conformation polymorphism (SSCP)

CASPASE FAMILY



https://en.wikipedia.org/wiki/Caspase_8#/media/File:Protein_CASP8_PDB_1f9e.png

LAST UPDETED:12/04/2017

Discussion

CASPASE FAMILY

They found that
the incidence of caspase-8
mutation in gastric cancer is
statistically higher than
those of

NSCLC
breast cancer,
and
acute leukaemias.

Furthermore, all of the 13
mutations detected
were in advanced gastric
cancers but not in early
gastric cancers

Discussion

CASPASE FAMILY

The mutations consisted of

1)three missense,

2)one in-frame deletion,
and

3)five frameshift mutations in the coding sequences;
……

4)two
mutations in the initiation codon;
……..

5)three mutations in the
introns; and one mutation in the 3V untranslated region

Discussion

CASPASE FAMILY

Pancreatic cancer is one of the leading causes of cancer related death in the world.

1)Smoking,

2)diabetes mellitus history,

3)alcohol drinking

are risk factors for pancreatic carcinogenesis

Discussion

CASPASE FAMILY

It has been shown that
pancreatic cancer cells
often present

1)non-functional CD95/Fas

2)and aberrant expression of FasL

and this mechanism may contribute to the malignant
and often rapid course of the disease

Discussion

CASPASE FAMILY

caspase-3 was mutated in one case in

1)stomach adenocarcinoma

2)one case in lung cancer,

3)four cases in colon cancer,

4)one case in hepatocellular carcinoma,

5)and one case in multiple myeloma

Discussion

CASPASE FAMILY

The mutations consisted of

1)six missense mutations,

2)four silent mutations,

3)two mutations in the introns,

4)one mutation in the 59-untranslated region,

5)and one mutation in the 39-untranslated region.

Discussion

CASPASE FAMILY

Caspase-9 is a virtually ubiquitous protease, constitutively expressed in a variety of fetal and adult human tissues

Mutational analysis

of caspase-9 was performed in neuroblastoma tissues

Discussion

CASPASE FAMILY

They isolated genomic DNAs from normal and tumour tissues of the same patients

Silent mutations were detected in two colorectal carcinomas and

one gastric carcinoma

Discussion

CASPASE FAMILY

In a case–control study,

lung cancer patients and age and gender matched healthy controls were investigated for caspase-9 promoter polymorphism in lung cancer

Discussion

CASPASE FAMILY

They reported that the -21263 GG genotype was associated with a significantly

decreased risk of lung cancer compared with the -21263 AA or the combined 21263 AA + AG genotype

Discussion

They found that caspase-9 polymorphisms were significantly associated with the risk of

CASPASE FAMILY

lung cancer in the smokers but not in the non-smokers, which reflects a gene–environment interaction

Discussion

CASPASE FAMILY

Such an interaction is biologically plausible because smoking is a major risk factor for lung cancer.

It was also found that the association between caspase-9 polymorphisms and the risk of lung cancer was statistically significant in the light smokers but not in the heavy Smokers(10)

Result

Most of what we know about apoptosis has been developed
and understood only recentlyThe core idea of designing therapeutic drugs for cancer is based on the fact that
worn out or damaged cells commit suicide in order for the body
to continue to grow normally, maintaining a healthy number of
cells, whereas this phenomenon is greatly disturbed in cancer
cells.

Result

we are still left with huge challenges to be overcome.
Development of drugs that act either by blocking the action of
antiapoptotic proteins, such as IAPs, small-molecule inhibitors
(antisense oligonucleotides),

Result

or by halting, hampering or
interference with the transcription of RNA, such as small
interfering RNA, BH3 mimetic and some HDACi, holds robust
potential for use in cancer therapy; however, the hope to cure
cancer is yet to be seen

References

1) **Apoptosis** in **cancer therapy**: crossing the threshold

2) **Apoptosis** in **cancer therapy**: crossing the threshold

3) Targeting **apoptosis** pathways in **cancer therapy**

4) The role of **apoptosis** in **cancer** development and treatment response

5) Bax plays a pivotal role in thapsigargin-induced apoptosis of human colon cancer HCT116 cells by controlling **Smac/Diablo** and **Omi/HtrA2** release from mitochondria

6) Apo2L/TRAIL: **apoptosis** signaling, biology, and potential for **cancer therapy**

7) **Oxidative stress** in end-stage renal disease: an emerging threat to patient outcome

8) Control of mitochondrial apoptosis by the **Bcl-2** family

9) The genetics of the p53 pathway, **apoptosis** and **cancer therapy**

10) … of **cancer** incidence, **mortality**, and **prevalence** across five continents: defining priorities to reduce **cancer** disparities in different geographic regions of the **world**